carbidopa-levodopa separated from at least one layer of immediate release carbidopa-levodopa by an excipient layer which may be drug-free and does not necessarily contain rate controlling polymers.

REMARKS

Objection to the Specification and Claims Rejection under 35 USC 112.

It is the Examiner's position "that the present invention's novelty lies with the release profile and its claimed ability to prevent fluctuations in plasma levels". On the other hand, the Applicant maintains that the present invention's novelty depends not upon the release profile per se nor upon preventing plasma level fluctuations (both of which have already been cited in the prior art), but rather upon the specific availability of novel formulations containing both rapid onset and sustained action carbidopa-levodopa that may be administered in tablet or capsule dosage forms. Parkinsonian patients require immediate and long lasting relief from their debilitating symptoms and cannot obtain such relief from presently marketed products.

The Examiner rejects Claims 4 and 10 "as being indefinite....." particularly in regard to the phrases "excipient layer" (Claim 4) and "adjacent to" (Claim 10). The Applicant uses the term "excipient layer" to represent a layer that may be drug-free, such as lactose, and does not necessarily contain rate-controlling polymeric material as claimed by Conte et al (US Pat. No. 5,738,874, April 14, 1998, collectively "Conte").

It is found in multilayer tablets as the layer that separates sustained release from immediate release layers. The term "adjacent to" refers to bilayer tablets or pellets in which the sustained release layer lies adjacent to the immediate release layer. The Examiner's constructive comments in this regard have been used to modify Claims 3, 4, 6, 7, 9 and 10 in the form of new Claims 11-16 to increase clarity and to sharpen focus in each of the affected claims.

The Examiner rejects Claims 1-10 "as containing subject matter not described in the specification". Applicant submits that guidance in applying the claimed therapy is provided on p. 3 which describes (1) a method usable by skilled artisans to obtain clinical resolution of Parkinson's disease and (2) a reference that discloses a clinical protocol enabling the skilled artisan to practice the claimed methods (JE Ahlskog, Hosp. Formul., 27:146, 1992). Pp. 3-5 contain passages describing the composition and manufacture of three examples of novel formulations. Thus, the present specification clearly and completely teaches how to make and use the invention. Accordingly, Applicant submits that the specification does comply with 35 USC 112 and respectfully requests withdrawal of this rejection.

Rejection of Claims 1-10 under 35 USC 103(a).

The Examiner rejects all claims "as being unpatentable over the combined teachings of Dempski et al (US Pat. No. 4,900,755, February 13,1990, collectively "Dempski") and Conte". Dempski discovered a controlled release form of carbidopa-levodopa

which prolonged pharmacologic activity and produced less variation in plasma levodopa levels than conventional carbidopa-levodopa (US Pat No. 4,900,755, col. 2, lines 18-42). The present invention summarizes these beneficial effects in the specification at pp. 1 and 2, but also identifies a flaw in the Dempski formulation, i.e., the serious delay in onset of action of controlled release carbidopa-levodopa. Correction of this flaw via formulations which combine rapid onset with controlled release carbidopa-levodopa is clearly set forth in the passage on p. 2, lines 13-29 of the present specification and in the examples on pp. 3-5.

Conte claims a 3-layer tablet containing immediate and slow drug release components. In his specification (col. 2, lines 3-6), Conte states that "the prior art does not envisage the possibility of obtaining products capable of releasing one or more drugs at different rates or else of releasing two different drugs sequentially". And yet the prior art contains numerous examples of one or more drugs released at different rates and of two drugs released sequentially. For example, Lin et al (J. Int. Med. Res. 10(2):126-128, 1982) describe the release of d-pseudoephedrine sulfate from the outer coat and inner core of a repeat action tablet and Nomeir et al (J. Clin. Pharmacol. 36(10):923-930, 1996) report on the sequential release from 2-layer tablets of immediate release loratadine followed by extended release pseudoephedrine. Could Conte have been unaware of the prior art that invalidates the novelty of his release profile?

The Examiner correctly indicates that Conte "teaches a pharmaceutical tablet capable of releasing one or more drugs at different release rates.....The first contains one or

more drugs with an immediate release profile and a second layer containing one or more drugs with a sustained release profile". But if the prior art covers this type of multiple release profile (see above), then Conte's novelty must lie elsewhere. The Examiner also states that "Conte teaches combination therapy with both levodopa and carbidopa in a formulation with multiple release profiles". Yet Conte cites no valid, rational or original reason to use a multiple release format for carbidopa-levodopa. Instead, he repeats well known and established text book versions which describe (1) the metabolism of levodopa to dopamine (US Pat. No. 5,738,874, col.2, lines 42-56) and (2) the use of carbidopa to inhibit peripheral decarboxylation of levodopa (US Pat. No. 5,738,874, col.2, lines 57-65) to support the need for sequential release of carbidopa-levodopa (Goodman and Gilman's The Pharmacological Basis of Therapeutics, Pergamon Press, New York,NY, 8th ED. pp 466-472, 1990). Therefore, neither Conte nor Dempski have recognized the problem solved by this invention, i.e., the rationale for immediate and long lasting therapeutic action of carbidopa-levodopa in Parkinson's disease. Recognition of an unrecognized problem militates for patentability.

If Conte's release rate profile and basis for utility are not novel, then the essence of his invention may relate to his formulations per se. In this regard the formulations of the present invention differ significantly from those of Conte. For example, Conte claims a 3-layer tablet consisting of a first layer containing immediate or controlled release drugs, a second layer containing one or more drugs either equal to or different from

the first layer and a third, rate-controlling barrier layer containing drug if necessary.

The present invention teaches a bilayer or multilayer tablet as well as a capsule dosage form containing pellets. The bilayer and pellet (capsule) dosage forms are not included in Conte's patent; moreover, they comprise a sustained release core of carbidopa-levodopa overcoated only with an immediate release layer of carbidopa-levodopa. In addition, the multilayer tablets of the present invention contain an excipient layer which, unlike Conte's third barrier layer, may be drug-free and does not necessarily contain rate-controlling polymers.

In view of the above amendments and response, Applicant submits that this application is in condition for allowance. Such action is respectfully requested.

Conditional Request for Constructive Assistance.

Applicant has amended the claims of this application so that they are proper, novel and unobvious. If for any reason, this application is not believed to be in full condition for allowance, Applicant respectfully requests suggestions of the Examiner pursuant to MPEP 706.03(d) and 707.07(j) in order that he can place this application in allowable condition as soon as possible and without the need for further proceedings.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231, on the date below.

Date: November 27, 1998 Alan Rubin